DRUG INFORMATION ASSOCIATION

FDA/DIA SCIENTIFIC WORKSHOP ON FOLLOW-ON PROTEIN PHARMACEUTICALS

BREAKOUT SESSION E:

IMMUNOGENICITY STUDIES

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M O D E R A T O R S

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P R O C E E D I N G S

DR. ROSENBERG: I think it's time to get started. So as we've heard this morning, immunogenicity is an important issue in the treatment of patients with biological therapeutics. And immunogenicity studies have been necessary, not only in the I&D phases and the licensing phases, but post-licensure as well, particularly following major manufacturing changes such as formulation changes.

We in the FDA have taken a risk-based approach to immunogenicity concerns. That's been elaborated in many articles and seminars, and a guidance document reflecting our views is in progress.

In today's breakout session, we hope to grapple with these issues that we think are most critical in formulating a policy for immunogenicity testing for follow-on therapeutics. While such testing is certainly necessary, the nature of such studies is under discussion.

So I'd like to start by introducing the

panel. I'm Amy Rosenberg, Director of the Division of Therapeutic Proteins in CDER/FDA.

DR. LOZIER: Jay Lozier, CBER, Division of Hematology.

DR. WOROBEC: Alexandra Worobec, CDER-06 [ph].

DR. STEIN: Katie Stein, MacroGenics.

DR. GERRARD: Terry Gerrard, TLG Consulting.

DR. ROSENBERG: Good. So I'd like to start--well, continue by going over the ground rules. So for ground rules, they're up here on the screen. Scientific issues will be examined; not legal or regulatory issues. The FDA moderator comments do not reflect agency policy; but rather, reflect the scientific concerns of the individual moderator. And industry moderators will identify whether their comments are representative of their industry organization.

The format that we've chosen will be a point-counterpoint discussion. About 22 minutes will be allotted for each question, though that may

change depending on the flow of things.

People in the audience may speak to the issue by providing data. And no more than five minutes will be allotted per individual. People must identify their affiliation. And following this meeting, the data that is given in oral form here should then be submitted to the agency, to this docket number that's up here on the screen. Moderators may present more specific questions to stimulate and focus discussion.

A word from our transcriber. When you get up to talk, please give your name and affiliation. And because it's sometimes difficult to catch that, please provide our transcriber with either your business card or your name and company written out on a piece of paper. That would be greatly helpful for her and for meeting documentation purposes.

So with that, I think we're ready to start. We decided we would just jump right in with the point-counterpoint questions. And we'll start with Katie Stein giving the point.

DR. STEIN: I'm going to start by reading

the point as you see it on the slide: Immunogenicity of protein products cannot be predicted by biochemical analytical techniques alone. Comparative side-by-side testing is needed. And the last point is that up-to-date methods should be used.

And I would just add, in addition--and we heard a wonderful introduction to the subject this morning--that there are minor components in the product that can affect the immunogenicity of that product. And I would posit that comparing the drug product is not the most sensitive way to detect these. And therefore, because a follow-on manufacturer doesn't have access to the drug substance that the innovator has, side-by-side testing will be needed to rule out contributions of these minor components.

And I would add, in terms of the up-to-date methods, of course, up-to-date analytical methods should be used. But also, up-to-date and well validated and sensitive assays should be used to measure the immunogenicity of a product.

I would say that even for the products that are out there and approved, as you heard during the clinical session, there are a variety of

settings which can affect the outcome of the immunogenicity of a product. And the heterogeneity of clinical settings, patient populations, dose, and route, all contribute to the aggregate immunogenicity nature of a product. And therefore, I believe that side-by-side testing should be done with accurate methods.

DR. GERRARD: And I'll start my counterpoint by actually agreeing with Katie that immunogenicity of protein products cannot be predicted by biochemical and analytical techniques alone. However, that's not what we're doing. What we're doing in the development of a biogeneric is a comparison. And the more you are like the innovator--structurally, physically, however you want to measure it, and biologically--the less likely there is a chance for immunogenicity.

So although the first statement is absolutely true in the development of a new

protein, we're talking about a follow-on, or a biogeneric.

Now, this actually puts a burden on the follow-on developer to do the more rigorous analytical tests that perhaps were never done with the innovator. Often, the innovator used tests that were appropriate at the time of approval; however, we know much more now. In other words, how many of the innovator proteins are really measured? Are they tested appropriately for aggregates, when we know so much more now about the analytical tests that are appropriate for measuring aggregates?

So they need to look at all of these things. And again, it's a comparison. You're comparing the innovator with the biogeneric. And if you are absolutely comparable in all of these facets, you should not have any greater immunogenicity.

DR. ROSENBERG: Okay. We can open this up to the floor. Please, again, use the microphones and identify yourself.

DR. NAKTINIS: Good afternoon, again. Vytautas Naktinis, Probios, but working for Teva right now.

So my first comment to get up maybe discussion would be addressing this morning's presentations on immunogenicity. What I missed both from the presentation of Dr. Thorpe and--sorry, I can't pronounce your name, as many people in the audience--is once the case stories were told about GMCSF showing where two different preparations are different in immunogenicity, as well as different Interferon-Alpha preparations are different in immunogenicity. It was no data presented to reflect what these particular preparations looked on physical chemical analytical characterization.

And I am very much aware about story with Interferon-Alpha 2, and I know that the simplest silver stain SDS page technique allowed already many, many years ago to identify [inaudible] adducts between human cell amalgam in Interferon-Alpha, which was actually the cause of

aggregation in those particular examples, sample studies.

To my memory, I think that GMCSF preparations "A" and "B," two different preparations, they also were different in physical chemical and biochemical characterization when simplest analytical procedures were applied.

So my question actually is: If you look backwards now to each immunogenicity case which is documented, can you trace to the factor which caused that? And I suppose you perhaps can. So if you can, so therefore analyzing finished formulation which is available from the drug store, you can identify those things. There are no mysteries around; should be factors behind the phenomenon.

And unfortunately, so far I heard only some kind of fear propagation around, rather than justification. What particular factors are causing immunogenicity--concrete, specific factors; not "if," not something "if." That's it. Thank you.

DR. ROSENBERG: Anybody like to respond?

DR. LOZIER: I can actually respond with one pretty well documented case. There was a factor-8 protein that was associated with an

outbreak, if you will, of inhibitor antibodies in patients who previously had not demonstrated these.

And the product--As I understand, the characteristics of the process were that it underwent heat treatment and solvent detergent viral inactivation. And by whatever mechanism, there was an extra cleavage in the protein that was identified at some point that seemed to be the problem that caused this.

DR. ROSENBERG: So I think one point is that it's easy in retrospect to look back and to say, "This is what was responsible." It's not so easy at the moment. It's taken, for instance, J&J many years to try and nail down the cause of the enhanced pure red cell aplasia.

By the same token, I think that there are some products for which you can't find reasons that you can nail to physical characteristics. So for Thrombpoetin, I think it has less to do with

aggregates than to do with the inherent immunogenicity of the molecule. For foreign proteins, aggregates may be completely irrelevant.

So I think there are some instances in which you can, in retrospect after a thorough study, go back and try and find the answer; and some that, as was mentioned for the human growth hormone--and I don't know if the fellow from Genentech is here who can speak to that--but an extensive search failed to reveal a physical cause for that immunogenicity.

[Simultaneous Discussion.]

MR. SHAW: Arthur Shaw, FDA/CDER; a small molecule reviewer.

Just a question of clarification, in terms of when you talk about comparing two products, and when you talk about the differences that can be seen. We certainly distinguish between specifications and characteristics in characterization. And it's not completely clear to me to what extent this is done in biologics. But it's certainly within the realm of possibility that

two products could meet specifications, but have different characteristics in terms of certain physical chemical characterization that is done more extensively when you do, say, a comparability.

To what extent is that an issue for biologics? I would imagine it is, but I want to make sure that it's clear. So that you can say that two products meet the specs, but only upon further investigation, which you might want to do for comparability, would differences show up.

DR. ROSENBERG: Would either of you like to take that on?

DR. GERRARD: But I think biologics face the same thing. I mean, I think you can meet specifications and still have product differences. But when you're talking, again, like making a manufacturing change or in characterization of a biogeneric, you're talking about probably going into much greater depth. And as I pointed out, the biogeneric has to meet today's standards, not the standards of 15 years ago, in the analytical techniques that they use.

DR. ROSENBERG: I think we're getting a little bit away from immunogenicity questions here. go ahead.

DR. NAVEH: David Naveh, Bayer.

I think that there is some obfuscation of two kinds of immunogenicity. One is the innate immunogenicity to a protein. And I'll just pick up on the example of Factor-8 in which about a third of the individuals that are hemophiliacs, they do not express Factor-8--that's why they are hemophiliacs--upon administration of Factor-8, develop antibodies which have significant ramifications. The blood did not clot when you give them Factor-8. And that's not the relevant immunogenicity for this discussion.

The relevant one is in PTPs; that means in "previously treated patients." Does the new product elicit immunogenicity in those individuals that got the original drug that did not show any antigenicity? So I think we should focus on that kind of antigenicity, in previously treated patients; not the innate one to the molecule.

And I'd like to hear comments on the question. And again, I think this batch of this Belgian product that you referred to is a good example. In that particular case, I believe that all the individuals that got this drug developed antibodies within about 20 to 40 days of receipt of

this Factor-8, and they were transient. That means they went away within a month or two.

So I'd like to ask the experts among you, like Katie perhaps. If one were to develop a follow-on drug that had this kind of new antigenicity, not the innate one, wouldn't you expect it to occur in most of those individuals that received the new drug? And this, of course, relates to the power number of tested subjects.

DR. STEIN: I'm not sure that I fully understand your question. And I guess, in terms of the Factor-8 deficient patient, the patient who doesn't make any Factor-8, the Factor-8 there is a foreign protein, in essence. So I wouldn't say there's necessarily innate immunogenicity to Factor-8.

Where there is innate immunogenicity, in some sense, is in monoclonal antibodies, where the idiotype--In that sense, maybe it's like a foreign protein, as well, where you're expressing a large amount of a particular idiotype that's normally expressed very much in the repertoire. There is some inherent immunogenicity related to the idiotype of a monoclonal, and you would expect that in a certain fraction of patients.

I can't directly--Maybe you could elaborate on the specific Factor-8 instance. But I would say, before you do that, that I'm not sure that you have to look at previously treated patients.

DR. NAVEH: Well, I think I'm not sure that the word "innate" was accurate from an immunologic standpoint. But it was relevant, because in the follow-on context you're not looking for the inherent antigenicity of a new protein; rather, would the follow-on product elicit antibodies to those patients that received the previous protein? When you discover a new protein,

you're trying to find out is this protein inherently or innately immunogenic.

DR. STEIN: I think that's hard to know.

DR. NAVEH: The context here is different. You are trying to weed out new antigenic sites in the follow-on product that could elicit antibodies. And this is not related, let's say, to--

DR. STEIN: Right, I understand that.

DR. NAVEH: Yes, that's what I was trying to--

DR. STEIN: I think it's very hard to predict. I think maybe Terry wants to comment.

DR. GERRARD: Well, I was going to say I think what you're referring to is like the case like Amy cited. Like with TPO [ph] there is something inherent in that molecule which made it antigenic. But the important thing is clinical trials did pick that up. That's not a marketed product. Therefore, that's not even a candidate for follow-on proteins. It was stopped in development appropriately.

I think what we have to recognize is that

for follow-on proteins you're going to have that ten to 15 years of clinical experience and immunogenicity before you even think about doing the successor.

DR. LOZIER: I can make a comment to that exact point, that the International Society for Thrombosis Hemostasis has recommended that new Factor-8 products be tested initially in the previously treated patients. And this has been our practice, to look at that as the key factor for a pivotal trial; although we do want the analysis in previously untreated patients.

And part of the issue is the signal, the noise ratio, is so much different in the previously treated patients. We're talking about a few percent may make an antibody with exposure, continuing exposure, to Factor-8 over a period of time, because you asymptotically approach a limit of what fraction will convert; whereas for the previously untreated patients, we're talking maybe 20 percent. And the variation there is so high that it's very hard to sort that out. So it has

been the recommendation to use previously treated patients, for that very reason.

DR. ROSENBERG: Yes. I'd like to, I think, steer us a little bit back towards the question and one of the issues. And I think this is a platform to do that. And we're talking now about what's the best way to test a follow-on for immunogenicity. And that gets back to the point, which is that comparative side-by-side testing is needed to look at the immunogenicity of a follow-on. So I'd like to sort of steer things back that way, because I think that's an important point. And here is certainly an alternative to a side-by-side testing schema. So comments on that?

DR. STEIN: Let me just add to Amy's point there. And that is that, again, as I said earlier, the data on the innovator products that's already out there comes from a variety of sources. And every sponsor has their own assay. And I don't think you can test a follow-on product in isolation and compare the data that you get to what's in the package insert for the innovator product.

I think that side-by-side testing will be needed. And the sera from those patients who were treated will need to be assayed in the same assay

that's sensitive and that can pick up antibodies to the products.

DR. ROSENBERG: Valerie?

DR. QUARMBY: Yes, Quarmby, Genentech.

I'd like to echo Dr. Stein's statement. I think it's absolutely key that head-to-head studies are done using the same methodology. We know from our experience and from reading literature that there are substantial differences between apparent sero-conversion rates that can be attributed solely to differences in antidrug antibody screening assay sensitivity. So I think it's only fair to use the same method to do these kinds of comparisons.

I would like to, if I could, just step back a little bit and mention that, in fact, I think there are two different kinds of characteristics that are liable to elicit immune responses. And some of those characteristics are related to the therapeutic; and so one might call

those intrinsic, if you will. Others are actually related to the context in which the therapeutic is used; so host cell factors, if you will.

And I think if we have very elegant analytical biochemistry techniques, we can actually nail down the molecular basis of some immune responses, getting back to the first question that came up. But thus far, we're not able to nail down in a molecular manner all of those causes--or epitopes, if you will.

And an example that we have from Genentech which Doctor--previously alluded to is the early development of Protropenome Met [ph] growth hormone. When we initially put batches of Met growth hormone into rhesus monkeys, and also into the clinic, we actually saw relatively high sero-conversion rates from that material.

We were able to improve our purification process and minimize the sero-conversion rates in our animal model, and also in the clinic. But despite a lot of time and effort that was put into analytical characterization of the similarities and

differences between the earlier and the older batches of material, we've never actually been able to nail down, again, on a chemical basis, exactly what the reason for that difference was. And those data are actually published in a "Biologics 2000" monograph.

DR. ROSENBERG: Thank you. Over here?

DR. SANDERS: Yes. My name is Steve Sanders. I'm a consultant.

I'd like the panel to address a question about head-to-head versus a single investigation of a follow-on product to characterize its immunology, if you would. If the follow-on manufacturer develops the appropriate antibody screens for its product, and characterizes the incidence of various antibodies that are formed to its product, and shows that those are comparable to what is known for the innovator, one, would that be a possibility?

And secondly, if that isn't a possibility, and you have to develop appropriate methods for both products and indeed do a head-to-head

comparison, and you find in your study that the innovator product differs substantially from the innovator's information, what impact does that have on the innovator's label?

DR. GERRARD: And that actually might be the case, because I think you're going to be held to today's standards. Some of the old antibody assays were appropriate at the time. In theory, I think a follow-on protein would only have to describe the antibody assays for their own product. However, because of the case you cite, you cannot compare antibody data from two different products for two different assays.

It may be advantageous for the follow-on protein developer to do both, just so that they have a basis of comparison with perhaps an assay that is far more sensitive than maybe the innovator used.

DR. ROSENBERG: Gene?

DR. KOREN: Eugen Koren, Amgen.

I have a question regarding Dr. Gerrard's statement that if we have two products, innovator

and follow-on, that are absolutely identical in terms of physical chemical and biochemical characteristics, that the immunogenicity testing would not be needed.

And it sounds good in theory, but we all know that in reality this is very highly hypothetical. I don't think you will have absolutely identical products. So the devil is in details.

If you could maybe answer, what would be the level of changes that you see that would trigger immunological testing? And I'm afraid that we start getting into this slippery slope: you know, of more difference, more testing, less difference, less testing. It's really unclear to me how to address this potential issue.

DR. GERRARD: I think we need to focus--I mean, we put that up there to be provocative, but I think we do need to focus more on those product attributes which do have an association with immunogenicity. And that's aggregation--Now, solubility may be the same thing as aggregation

when you look at it. Three-dimensional structure. Those types of attributes.

DR. ROSENBERG: Alan?

DR. LISS: Alan Liss, Barr DuraMed.

We've heard a lot about the various experiences that the innovator companies have had from their years of experience. But has the FDA learned anything about what triggers immunogenicity from the many failures--or few failures; I don't mean to offend anybody--that may have happened lot to lot? And I don't imagine this would be shared; shouldn't be shared. But should that give the FDA some historical background on the kinds of quality attributes that one should look at?

And then a second question to that, from what I hear from a lot of people--and I certainly would challenge this--are we also saying that to do the right thing every comparability change should trigger an immunogenicity study?

So, you know, it's a matter of: Where do we draw the line? And can we not only make follow-on products, but can we learn something from

the experience that, hopefully, has been shared with the FDA?

DR. ROSENBERG: I'll take a crack at that. I think basically we apply our risk-based strategy towards those kinds of evaluations. And, yes, certainly, we've had examples where certain physical chemical characteristics have been associated with immunogenicity, and others where we didn't know what the cause was.

For comparability following manufacturing changes, we apply a risk-based approach. So if you have a product that we consider high risk for hypersensitivity, the more dire sort of circumstances, for neutralizing not only the product but the endogenous molecule that mediates a biologically unique function, we are very likely to ask--and we have asked--for immunogenicity studies, as well as other safety and efficacy studies following changes to those products.

I want to finish up with Inger's comments, and then move on to the next question.

MS. MOLLERUP: Thank you. Inger Mollerup,

Novo Nordisk.

Staying on the question of side-by-side comparisons, I think there's one issue related to the aggregates and the immunogenicity of our protein of interest, per se.

But there's a different category of impurities that I think we also need to consider that basically relate back to the uniqueness of the manufacturing process; in that we take a string of DNA and put it into a cell line. And that DNA, with a leader sequence of some sort, being put into the DNA somewhere, there will always be mis-clipped forms. There will be product related impurities with extensions, with absolutely foreign amino acid sequences. And I think these are also some of the products that come into the risk assessment for immunogenicity.

And so far, I think we are certainly able to identify those in HPLC assays. We're able to reduce them to limits below what's detectable in HPLC assays. But we haven't so far heard that that level is an appropriate level where, if we're below

that one, there's no risk of immunogenicity. So I think these trace amounts of impurities that will normally be way below 0.1 percent certainly need some consideration. Do we have any idea of how low do we have to go to be safe?

DR. ROSENBERG: That's a very good question. Does anybody want to take a crack at it?

DR. STEIN: Well, I think that's the issue. We don't know.

DR. GERRARD: We don't know.

DR. ROSENBERG: Okay. You know, this question clearly--Hopefully, we'll be able to come back to it. But we do need to move on, to be sure we cover all of the questions.

So the question is: Are animal studies useful in predicting relative immunogenicity; i.e., in comparing innovator and follow-on proteins?

Katie, please take the point.

DR. STEIN: Animal studies comparing immunogenicity are helpful in elucidating potential differences in product immunogenicity, but are not sufficient. Clinical studies are necessary.

I would say that one of the areas where animal studies are useful is ruling out new antigenic determinants. One can take an innovator

product and a follow-on product and immunize animals where you know you're going to get antibodies, and then show that all the antibodies made against the follow-on can be absorbed by the innovator; showing that there are no new antigenic determinants that are expressed there. But that is not sufficient, I think, in giving you the answer. It will allow you to perhaps do reduced immunogenicity studies in the clinic.

Obviously, if you see big differences, then you might want to stop right there. But if you don't see differences, then you would move on to a small clinical trial. And the size of that would again depend on the product and the clinical study.

DR. GERRARD: Okay. And the counter to that is we all know that animals are not predictive of immunogenicity. But here we're not asking is it predictive, but you're just comparing "A" versus

"B." And if they are not significantly different compared to the innovator, and there's no new antigenic determinants that are seen in animals, we're not suggesting that immunogenicity studies not be done, but could they be done post-marketing?

So you have some assurance in comparing "A" versus "B." You are not seeing any new antigenic epitopes. You are going to do immunogenicity studies, but can you do them post-approval, when actually you might be able to look at a larger sample size than the typical 50-patient study which may not tell you much pre-approval?

DR. ROSENBERG: So Terry, the point was made, just in terms of titers here. But do you mean overall similarity? For instance, the time course of development? So you're not just referring specifically to titer?

DR. GERRARD: Right. No, no, no. I mean, I think that if you do an extensive animal study, it should be able to buy you something. In other words, you know, and do a thorough--Not just look

at titer; but to look at titer, time course, antigenic epitopes, so that you are doing a thorough investigation, and you don't see anything new. Then perhaps you can put this off to post-marketing.

DR. ROSENBERG: Okay. Opinions on this?

DR. STEIN: While people are coming to the microphone--

DR. ROSENBERG: Is this a post-prandial daze?

[Laughter.]

DR. STEIN: I would just say that titer alone isn't sufficient. You have to look at the actual quality of the antibody. What epitope does it see, and is it neutralizing? And so just titer is not sufficient.

You could use titer, even in a clinical setting, as a basis for further exploring; so that high-titered antibodies would then be studied for neutralization. Obviously, very low or background level titers would not necessarily be.

DR. MAIA: Mauricio Maia, from Genentech.

I agree with Dr. Stein's point. And if we sort of take a look and think about what was said in this morning's session about the number of

patients that would be needed just to show an equivalence or a similarity with a product in terms of efficacy within a 10 percent range, we're talking about hundreds; maybe 800 to several thousand patients if you get down to the 5 percent range. So potentially, we could be talking about several hundred animals.

But that was just for one factor, a plus or minus. And if you take that into the context of immunogenicity, you could be looking at how many animals develop antibody versus animals that did not develop antibody. If you look at this from the complexity or the context that it needs to be looked at in terms of titer, just like Dr. Stein just mentioned, whether or not those animals are developing neutralizing antibodies, you could potentially be talking about several thousand animals.

Now, I think this is not even the main

issue. It's not even the point. The point is that there is very clear indication, very clear evidence out there that animal studies, animal models, are not predictive of what we'll see in clinical studies. So you could potentially be treating several thousand animals just so that you can show some level of similarity, and then come up with a conclusion that is misleading. Because it will not in every case--and probably not even the majority of the cases--reflect what you would see if you treated the same number of patients.

DR. STEIN: Let me just say that animal studies are not a substitute for human immunogenicity studies, and they never will be. There isn't an animal that has an identical immune response to humans. And so you have to put these products into humans to really know what the immunogenicity is.

But I would argue that you can show--If you do limited animal studies where the products are known to be immunogenic, you can look at whether there are new determinants there. And it's

useful for ruling that out. If you were a follow-on manufacturer and your product stimulated antibodies to new determinants that were never seen with the innovator product, I would be concerned about moving forward with that product as a manufacturer.

DR. GERRARD: I mean, we're talking about animal studies as a way of giving you information to reduce risk. And although they are not predictive, when you do a comparison, is that helpful? Now, the caveat here is that this is going to be very difficult to validate, as far as two different proteins. Because if you find a protein in animal studies that is more immunogenic than the innovator, chances are you're not going to pursue that development.

DR. MAIA: Right. And I think that sort of mirrors some of the comments that we had in the clinical pharmacology session yesterday, including from a colleague from Genentech; that when we see a big problem in animal studies, then we raise the concern level. The absence of a problem does not

mean that there is no problem.

DR. GERRARD: That's right.

DR. MAIA: So again, I go back to my point. If you want to have a statistical significance in comparing those two products in the multi-dimensional context of immunogenicity, you could actually potentially be talking about several thousand animals; and then come up with just ruling out that there is a major problem in animals. Because as far as I know, I mean, there is no indication or population of patients that reflects the immune system of synomologous monkeys or any other non-human primates.

DR. STEIN: I can't imagine any setting that would require thousands of animals to compare the immunogenicity. Those products are all very immunogenic in animals and, depending on the species, they are more or less immunogenic. And relatively small numbers of animals could allow you to compare the qualitative response as well as the quantitative response.

DR. ROSENBERG: Alexandra, did you want to

comment?

DR. WOROBEC: Yes, I've got a comment. I think what actually brings this issue to fore is also the system that you're operating in; meaning whether or not the innovator product had extensive animal testing and whether a good animal model was identified for that particular product. I think that's very essential in trying to decide whether or not using this approach is going to yield fruitful data.

If there is that type of information, clearly, one can rely on such an animal model. If it was looked at in multiple species and not identified, I think that makes the task that much harder, and perhaps even impossible. Where there was not extensive testing done and no immunogenicity issues were defined, we still don't know.

So I think there are different ways, different levels of looking at it, depending on what we know about the particular product's--if you want to call it a "work-up"--in the past in terms

of immunogenicity testing.

DR. ROSENBERG: Alan. And please, let's not lose sight of the fact that in this question it's the issue of how much pre-marketing and how much post-marketing. So, Alan?

DR. LISS: Sure. Very good; bring us back to point. Certainly, I would definitely think that there are very few animals, if ever, that we will find that can be predictive pre-marketing for immunogenicity in humans.

But I would like to say that it's our challenge to use these animals as amino analytical tools to give us more information; as much as possible, to help this whole picture of the characterization from the purest chemical to the most biological possible; to help us direct and limit our clinical trials so that we do our clinical trials with the least amount of people exposed as possible. Pre-marketing, if necessary; and certainly robustly back this up with our post-marketing. But immunology in animals has a place, but it's not a predictive place.

DR. GREEN: Jim Green, Biogen Idec.

In fact, this issue was talked about quite a bit at the pharm-tox session yesterday. And in

fact, I'm actually buoyed to hear some of the positive comments about animal testing here, because all I hear usually at these sessions is how unpredictive they are.

And one thing with generalizations is that you can always find exceptions which prove the generalization wrong. And I think it's particularly true in this case, because we do know that in many cases the way we make protein molecules today, for reasons that we don't fully understand, in [inaudible] of animal models, they're non-immunogenic. I mean, they just are. It's case by case.

So with the question that was put forth here: In some type of head-to-head comparison, could you envision utility of animal models to predict, or increase, or decrease the level of concern that might translate to how concerned would you be in the clinic? I think you can.

And an example that I would give you would be one that I think many companies have that are involved in humanized antibodies. For reasons that we don't fully understand, for example, but we have many--or several--that we've tested long times in primates that are remarkably non-immunogenic. The

profile essentially that they end up showing in humans is also non-immunogenic. So essentially, that's the baseline that you have to work from.

Now, if you were a follow-on company coming out to make that same protein, I could envision some type of head-to-head comparison where if you had that baseline established and you're testing the innovator's product and it shows a rate, let's say, of 5 percent in animals, and the rate essentially in the follow-on product was 25 percent, I would think that signal should be looked at. And I think it would be a cause for concern early, and it should have some type of translation to the clinical setting.

DR. ROSENBERG: Jim, can I just ask you a question? Where you saw non-immunogenicity in the

primates as well as humans, were those for antibodies that were immunosuppressive or immunomodulatory?

DR. GREEN: One was.

DR. ROSENBERG: One?

DR. GREEN: Right.

DR. ROSENBERG: The other was not?

DR. GREEN: No. I mean, different mechanism of action. But I think the issue here is the generalizations. And I think many of the generalizations that deal with protein immunogenicity were established very early on with some of the Interferons and, in fact, with the growth hormones. And much of the work that was done in animals in those particular settings was done without realizing that these things were blocking. And in fact, a lot of work was done that was really highly irrelevant, essentially, to the ultimate conclusions.

However, since that point in time, many of these proteins are very well conserved. They are active in a variety of species. They give a

variety of antibody responses. So I think to totally dismiss those categorically is wrong. And in certain cases, they can provide, I think, useful insight to detecting differences, as Dr. Stein indicated.

DR. ROSENBERG: Yes. I think in regard of that, the immunomodulatory properties of your protein are important. So proteins may have activity in your non-human primates, but will not have activities in lower species. And so in terms of looking at comparative--or looking for generation of new epitopes, you might have to go to lower animal species.

Jay?

DR. SIEGEL: Siegel, Centocor.

I'm at a loss here. I don't understand the counterpoint, or the argument behind it. The counterpoint presumes--and I think correctly--that you want to do the clinical study. And it asks whether to do it pre- pr post-marketing.

Well, if we assume you want to do the study, and we assume you want to do the study

because there is a risk, there is a risk that immunogenicity will be different and that can translate into loss of efficacy, into safety concerns, and into immune complex type concerns, and you know you can learn a lot from even studying a few dozen or a couple hundred patients so you agree you have a need to do that, why go to the market and expose thousands of people to that risk before doing the study, if you're going to do the study anyhow? Maybe somebody can explain why that would make sense. There is already a drug out there. It's not like there is an unmet medical need. Why would you do that?

DR. GERRARD: I think the question is: Will the animal studies, thorough animal studies, reduce the risk enough so that you would feel comfortable marketing it? And I would say, in most cases, yes, certainly. That there is not a risk--

DR. SIEGEL: Well, I would say, for those who believe it, then don't do the immunogenicity studies. I find that a hard position to support but--

DR. GERRARD: Well, that may be appropriate, too.

DR. SIEGEL: If you need to do them, why

not do them?

DR. GERRARD: But that could be true of any phase four post-marketing study that the FDA requests. I mean, there may be unresolved issues. And the immunogenicity studies may be at that point just confirmatory that there is no increased risk of immunogenicity; rather than asking a new question.

DR. SIEGEL: I would just argue that in most cases with phase four studies, to complete them prior to approval would both have a substantial, in some cases, delay on approval and, in other cases, would have a negative impact--or in some of the same cases, as well--because of the lack of availability of a drug.

I think here that--Well, I suppose if you think that there's almost no chance there is going to be a problem, but you want to find out anyhow for safety, you could come to that conclusion.

DR. GERRARD: Right. And I think the reason--

DR. SIEGEL: It is hard to find where the database is to come to that conclusion.

DR. GERRARD: And you may need something for the label. And I think it's sometimes a

practical issue that you may need something for labeling. But I think the risk would be minimal, absolutely.

DR. SIEGEL: So you would actually take such a drug before the immunogenicity data were around, huh?

DR. GERRARD: I would. There are lots of marketed drugs where very little immunogenicity studies were done before approval. Right?

DR. SIEGEL: Right, but in this case there are some [inaudible].

DR. GERRARD: Right.

DR. NAVEH: David Naveh.

I think that the biogeneric industry is playing a very dangerous game. This is the biggest risk. I think it's been shown in many of the

previous presentations, animal studies do not predict with fidelity. And even in those cases that were talked about--this Belgian manufacturer of factor-8--although you could see an extra band on the SPS page, that was in retrospective analysis. You would never be able to predict which change and at what quantity would elicit an immune response. In my own opinion, this is the biggest risk.

What I was trying to say before is, if you have a protein that innately--pardon, you know, the English--elicits 7 percent antibodies, that's not what's relevant. And for that you would need a very high-powered study. What's relevant is if you changed to a different manufacturer--That 7 percent is part of the drug itself. You're looking for the other antigenicity that would be elicited. And I was trying to say that I think that if you have that you would see that in fairly limited clinical trials. And they should be done pre-marketing.

I just had two questions to the panel. One is regarding which kind of patients would you

select? Would they be naive patients, or previously treated patients?

And the second is head-to-head versus absolute. For new drugs that are multi-sourced--which exists today--you are not required to do head-to-head comparisons. You compare against historical. So I think I'm curious on the comments of the panel on that.

DR. ROSENBERG: I could just speak to that last point that you made; which is that that's true, but they have stand-alone BLA's. They have done extensive safety and efficacy and immunogenicity studies. And the clinical consequences of whatever immunogenicity you have seen is understood. For follow-ons, you're looking for reduced clinical testing. And part of that is reduced immunogenicity testing. So that's, I think, what drives the need for a comparator.

If you want to come in with a stand-alone BLA and do all of the studies and get a very robust experience pre-marketing, that's fine. And that may be appropriate for some agents which have

readily detectable clinical end-points. It might be easier to go that way. But if you're looking at a follow-on situation where there is going to be less clinical testing, then a comparative trial may be what's essential.

DR. STEIN: To answer the question about patient populations, I don't think you could limit one or the other. The product is likely to go into both patient populations.

DR. NAVEH: No, of course. But I think that I was trying to--First of all, I am not for anything; I just think this is the biggest risk, antigenicity.

But from a strategic standpoint, you would first check out whether previously treated patients exhibit this. And once you showed that this did not happen, you would then move into naive patients.

DR. STEIN: Well, and certainly it might be sequential, yes.

DR. GERRARD: One of the things, I wanted to get back to address Jay's question. I think,

even for innovator proteins the idea that we can understand immunogenicity pre-approval in a study of anywhere from several hundred to maybe a thousand patients is probably naive. We don't.

And can we expect a follow-on protein to completely understand immunogenicity pre-approval? No. Oftentimes, we don't understand immunogenicity completely for many years. But that's the advantage to the follow-on, is that they have years of experience. You know, you're not starting out with a new patient population, or a new dose, or a new route. You have the extensive clinical history, the patient history, to understand the basis of immunogenicity.

DR. ROSENBERG: Jay, if you'll respond to that? And then we need to move on to the next question.

DR. SIEGEL: Yes, I would like to respond to that by also responding to another comment. Someone just commented that what mattered wasn't so much whether it was the 7 percent immunogenicity the same, but whether there was new or different

immunogenicity. What matters is not whether there is immunogenicity at all. What matters is what its impact is on the safety and the efficacy of the drug.

So in answer to Terry's comment, I would simply say that with the innovator product, you're right, we don't understand this immunogenicity at the time of licensing; but we do have data showing that it's safe and effective. Now, with the follow-on product, we're trying to make a presumption that without those data showing that it's safe and effective, we can assume it has the same safety and efficacy as the innovator.

If we're going to make that assumption, we'd better well be darned sure it has the same immunogenicity as the innovator. And my own personal opinion is animal models and characterization just don't get you there.

DR. ROSENBERG: I think that's a good lead-in for the next question. So let's make the point about immunogenicity clinical studies.

DR. STEIN: The design of immunogenicity

studies should take into account the product and patient factors that bear on immunogenicity; including the immunogenicity history of the innovator, probability of immune response, as well as the potential consequences of anti-product antibody formation.

Consequences of antibody formation include effects on safety and loss of effect of the product. Duration of the immune response should also be considered, evidence of possible tolerance and, in some instances, a diminution of the antibody response to the product over time. This certainly has been noted with a number of monoclonal antibodies. And should also consider products with little risk of hypersensitivity responses.

DR. GERRARD: Actually, what it says up here is regardless of the immunogenicity of the innovator product, most clinical immunogenicity data should be collected post-marketing. I would almost say that because of the immunogenicity of the innovator product, because you have that

extensive history, the molecule and the patient population and how that behaves, that you could do most of this post-marketing.

DR. STEIN: I'm sure there are a lot of people out there with data that bear on this question. Would anybody like to get up and give us a little data?

Are you coming to the microphone? Yes. Good.

DR. DILIBERTI: Coming to the microphone. Charlie Diliberti, Barr Labs.

There are a number of currently marketed brand products for which the manufacturer has either not conducted immunogenicity studies at all, or those immunogenicity studies have been deemed to be not adequate.

For example, Abbokinase [ph], I quote from the package insert: "The immunogenicity of Abbokinase has not been studied." For Aranesp [ph], Neulasta [ph], Xygris [ph], and Evastin [ph], as some additional examples, all have packaging insert statements to the effect that the

incidence of antibody development receiving that particular drug has not been adequately determined.

For products such as this, in light of the previous dialogue that we've heard, both at the September meeting and over the past two days, to the effect that even small changes in the process can create catastrophic problems within immunogenicity and these problems may not be detected analytically, how can the agency justify allowing process changes for these products? That's the first question.

And the second question is: For products such as this, where the innovator either has not done immunogenicity studies or they have been deemed not to be adequate, should there be perhaps a different sort of standard that the, quote-unquote, follow-on manufacturer would be held to, so as not to create the unfair situation of the follow-on manufacturer having a greater burden than the original manufacturer?

DR. ROSENBERG: I'll start off with that. I think that in those cases where the label states

that it hasn't been adequately evaluated, we have obtained, certainly, phase four commitments for looking at better assays. But the advantage that those companies have is that they have an extensive safety and efficacy evaluation of patients pre-marketing. And so even though the assays may not have been tweaked to the level we would have liked them to be tweaked, and that's what we're asking for, we have a very high confidence that we can describe the risk using those products, as well as how immunogenicity may impact on it.

So I think for the innovator coming in who wants to do less clinical testing--I mean for the follow-on who wants to do less clinical testing and has less robust experience, then that's relatively problematic.

It gets back to something that Jay was talking about. I mean, it's even potentially an ethical issue. You have a safe and effective product based on clinical experience. We'd like to see a better assay. We'd like to have those tweaked up. But we have great confidence when we

release those products. The same may not be true unless you have an extensive clinical safety and efficacy database.

DR. STEIN: I would just add on the issue of product changes, in my 22 years at the FDA I can tell you that there were many companies where product changes were made, where a company was asked to go back and do additional clinical studies. This information would not always be public. It would be part of a supplement to their license application, and it would be data requested by the FDA to ensure that the product was safe to market as a changed product. You would not necessarily know about these, but I can tell you that there were many such cases.

DR. ROSENBERG: Yes, absolutely. In fact, for a high-risk product when the formulation was changed, we had a thousand-patient immunogenicity study done for a high-risk product; this for manufacturing changes. So we do ask for those studies; as well, sometimes, for additional clinical safety and efficacy studies.

DR. GERRARD: But there are certainly instances present where they don't require any new data, and certainly no immunogenicity data, as

well.

DR. STEIN: But there I would argue again, that depends not only on the change, but on the side-by-side comparisons of the new product with the old, using the same assays and the same reference standards. So that the body of data to support the fact that those products are not changed would be considerably different than the situation with a follow-on where there is no access to the internal reference standard and where the assays are different as well as the process being different.

DR. DILIBERTI: But then we're back to the situation of relying on the ability of the analytical tools to detect changes that could elicit immune responses.

DR. STEIN: When you do side-by-side comparisons with a high level of sensitivity and an internal reference standard and assays that have

not changed, you have a higher degree of certainty.

DR. DILIBERTI: Thank you.

DR. ROSENBERG: Valerie?

DR. QUARMBY: Quarmby, Genentech.

I'd just like to comment briefly on the product insert information on Evastin. The data that was just quoted arose as a consequence of the fact that we weren't able to wash patients out with Evastin for more than a fairly short period of time. This is because these patients were terminally ill, and it was not deemed ethical to wash patients out for a very long period of time, to the point where there was not enough drug onboard to interfere with our screening method.

So I'd like to clarify, we did actually screen for antidrug antibodies, but there is this technical challenge there. It was, in this particular case, sort of ethically--We were ethically unable to comply with that.

I'd also like to just comment in general that I agree with the points that were raised here by Dr. Stein. And I think it's really important to

assess immunogenicity data in the clinic. And I think it's really important to acquire that data in the context of safety and efficacy information, as well, so that you can actually look at the immunogenicity data in the context of the clinical database.

I think it's really important to acquire much data pre-approval, to minimize the risk of exposing the general population to a product that may be immunogenic, and to establish at least some preliminary information on sero-conversion and potential clinical sequelae.

Clearly, these studies need to be done pre-approval. And I think they have to be powered appropriately. And of course, post-approval surveillance is also really important, to look for rare events.

I would like to also comment that at Genentech we certainly put a lot of time and effort into designing our antidrug antibody screening and characterization strategies. And it's not clear to me why follow-on biologics manufacturers should be

held to different standards.

DR. GERRARD: I don't think anybody expects them to be held to lower standards. They would certainly have to have all the same validated assays, and their antibody detection assays would have to be just as stringent.

DR. QUARMBY: But I think you're also saying that, in fact, in your review it's not important to look for immunogenicity prior to licensure.

DR. GERRARD: No, it's important to minimize risk. Risk can be minimized by analytical comparisons and by doing comparisons in animal models. And that's a way of minimizing risk.

DR. QUARMBY: But I think it's been fairly clear from the analytical biochemical presentations, and also from the discussion of animal models, that it's actually not possible to predict risk of immunogenicity in absolute terms from either of those data sets.

DR. GERRARD: I disagree.

DR. ROSENBERG: Alan?

DR. LISS: I'd like to agree with the last speaker that, certainly, the generic industry should not be held to any lower standards than the

innovator. And I don't think it's ever anybody's intention. Certainly, in the context of a risk-benefit analysis--and I think we should never forget that--the concept, I think, from day one we've been talking about is assembling as much information as possible, to limit the uncertainties.

And as we progress, nowhere do we think of shortcuts--shortcuts just for the heck of it. It has to be based on strong science and knowledge and support of what we can get from the literature, as well as what we may have to garner from head-to-head studies.

I think the challenge, always, is not just to do a knee-jerk, reflex study for no apparent end point, and to get smarter in designing these clinical studies. Because I really think immunogenicity for the products already in the market is a scary bag of unknowns, both for

innovators and for the biogeneric people. We have to be better immunologists; ask smarter questions.

DR. ROSENBERG: Well, another part of that question was the duration of the immune response. So we know from treatment with multiple therapeutic proteins that even though antibodies are made--and some of these are in fact neutralizing--that they do appear to disappear over time. Does this need to be studied, as well? And how best to study that?

So if an innovator product--Say for a therapeutic enzyme you get an antibody response of 15 or 20 percent, and then that over the subsequent year diminishes to 2 to 3 percent, is it important for the follow-on to be studying that, as well? So not only looking at the induction of antibody responses, the type of antibody responses, but their duration and the reimposition of tolerance. Anybody want to speak to that?

DR. LISS: Yes. I agree. I mean, again, this just goes to the same principle. We have to look at clinical relevance, obviously. And we have

to learn more about all of our products. I mean, this is not something--You know, we talked about safety and ethics and so forth. Everyone is making products for our children, our grandchildren, and our parents and ourselves to use. So we need to do what's right.

We need to both use logical science, clinical relevance, and a solid regulatory path, to move forward with all of these products. So case-by-case, but that certainly sounds like something that has a lot of scientific merit.

DR. STEIN: I think in some instances the diminution of the antibody response over time is also associated with the diminution of side effects of the product--injection site reactions, or infusion reactions that go away. The exact origin isn't fully understood. And in some instances, I think that was probably a tip-off to the fact that the immune response was waning. I don't know whether Jay wants to comment on that point.

DR. ROSENBERG: Okay. I think we can move on. The last question in some ways recapitulates

the discussion we've already had, which is really regarding the necessity for comparative side-by-side testing to compare immunogenicity. And so I think we did truncate that a little, in the interest of making sure we covered all aspects of the questions. But I think we can come back to this question at this point. So Katie, would you like to take and embellish this?

DR. STEIN: Sure. Well, again, this is a recapitulation. Given the differences and key attributes of antibody assays, reduced clinical testing overall for follow-on products, comparative side-by-side testing is necessary to compare immunogenicity. And then addressing the question, you know, what designs would be appropriate? And I'd certainly like to hear opinions from the audience.

DR. GERRARD: And I think I can argue with myself on the last one. I don't think it's essential to compare immunogenicity of the innovator and the follow-on directly. A single-arm immunogenicity study of the follow-on may be

adequate.

But on the other hand, I think that we could be talking about two different things. When you're talking about--I think it's an advantage to perhaps the follow-on developer to do a side-by-side comparison only because they are using the same assay or the same type of assay to analyze both products side-by-side. So that if you were to see higher immunogenicity, is it really because the product is more antigenic, or is it because your assay is better than the innovator's? And we know we can't really compare across assays. So comparing in like assays may be an advantage.

I think where we get into trouble is when we're asking the follow-on developer to do a trial that is not just a descriptive trial for immunogenicity, but that's large enough and powered enough to see differences in immunogenicity. And that far exceeds what we're requiring of the innovators.

If we're talking about, say, an immunogenicity rate of, say, 20 to 30 percent, and

perhaps you're expecting the follow-on to be a 5 percent difference, that's a huge clinical trial to see a delta of 5 percent or less. And that may not be worth doing.

DR. STEIN: Let me raise the issue about side-by-side testing in the context of monoclonal antibodies. We haven't heard much. And maybe the generic drug industry is not interested in making generic monoclonals--which, as a monoclonal manufacturer, that's okay with me.

[Laughter.]

DR. STEIN: But the issue there is detecting antibodies to a product that is itself an antibody. And it's fraught with technical problems. And usually, a manufacturer will have to develop an anti-idiotypic antibody to capture the product from the serum and then use the anti- idiotypic antibody again in some type of sandwich assay. And circulating product itself interferes with these assays.

And so I think we heard that mentioned in the context of Evastin. But I think when you have

an assay for product antibodies that is so unique to that product that it is an anti-antitypic antibody-based assay, I think it's going to be imperative that side-by-side comparisons are done; and with whatever assay is developed by the follow-on manufacturer, looking at immunogenicity against the follow-on and the innovator product.

DR. ROSENBERG: Valerie?

DR. QUARMBY: Quarmby, Genentech.

I totally agree with Dr. Stein's point here, and I think it's really important that we do head-to-head evaluations of immunogenicities in the same patient population, the same methods, and so on and so forth.

And as we all know from quotes in many product inserts, it's really not possible to compare immunogenicity data across methods at all. Dr. Stein already alluded to this. But again, I think it's really key.

I think it's important also to be powering our studies adequately to assess sero-conversion rates correctly. And for innovator products, with

incidences of 1 or 5 percent, again, I think it will be really key for a follow-on biologics manufacturer to show non-inferiority.

I think it's also important to realize that it's not sufficient just to be tracking sero-conversion rates and antidrug antibody titers. I think it's also important to be tracking characterization of these immune responses, too.

And so, to quote a hypothetical example here, if you'd had two biologics that were being used in the same context, if you will, and they both had 5 percent sero-conversion rates, with modest titer antibodies, you're looking at two very different scenarios, if one of those situations is 5 percent neutralizing antibodies, and 5 percent is a situation where there are no clinical sequelae at all. And I think we've run into that, and this was described earlier on this morning in the context of Beta Interferons.

But I think, again, it's really important, if we're trying to establish that follow-on biologics are in fact comparable to innovator

products, that we have all of this information available; and preferably, information available prior to licensure, as opposed to acquired post-marketing.

DR. WOROBEC: I have a question for you, Valerie. Would you advocate then doing PK testing in such a trial, to look at effects on levels of your product?

DR. QUARMBY: Absolutely. Yes. And I actually mentioned that in my earlier discussion of the point directly previous to this. I think immunogenicity data should actually be acquired not just in the context of the trial that's run solely to look for immunogenicity; I think actually it should be acquired within the context of studies that are really looking at clinical safety and efficacy, too.

So that if you're seeing immune responses, you are able to actually look at them relative to your clinical safety databases, to get a sense of whether in fact they are impactful or not. And it's not clear to me how you would make those

connections in the absence of an adequate safety database on well designed studies prior to marketing.

DR. GERRARD: You have an adequate safety database, generated by the innovator.

DR. QUARMBY: Yes, but the challenge there is that the innovator's safety database is relative to that product and that process.

DR. GERRARD: I think that we've dropped the--"The process is the product" is an old, old biologics mantra that no longer exists.

DR. QUARMBY: I would beg to differ. I think that in fact it's very hard to compare drugs that are made by different processes.

DR. GERRARD: Now, you can change the process, and still have the same product. We crossed that bridge years ago.

DR. QUARMBY: No. Our experience, even in transferring the same process from our South City manufacturing plant to Vaccaville would suggest that that's absolutely not the case.

DR. SIEGEL: Coming back to head-to-head

comparisons of antibodies specifically, there is an unfortunate history in the biotech industry of companies in marketing efforts competing by comparing immunogenicity rates of different products related for the same indication, based on different studies, with different assays.

And it's indeed a sad history. And at one point in that history, I remember well getting a call from somebody doing the assays at his company, and he gave me a long list of the various steps his company had taken to reduce their immunogenicity rates.

You can make an assay give a lot of different results, especially this sort of assay. And that's just the assay. Suffice to say, we know from a variety of products--Remicade [ph], one of our products--that the concomitant medications the patient is on tremendously influence the immunogenicity. The dose of the product: The higher the dose, the more frequently you give it, the lower the immunogenicity. And populations across trials differ, even when the entry criteria

are the same.

So if you're going to get any meaningful comparator data, you have to do it head-to-head. What assay you do it in, I think, is an interesting question. I think what we learned from this morning's speakers is that you probably want to be doing a number of assays, looking for different types of antibodies with different activities.

I would note, in particular, a concern raised by a question I made then, that if you just look for antibody to the innovator product, or even a natural product, you have at least one residual concern, which is that the new product could be folded or in some way present a neo-antigen that isn't present on the other product. That could be immunogenic. It could give rise to that neo-antigen. And you might not see it in an assay, except with using that product itself as the target. So I would suggest that at least one of the assays that need to be done should include the new product as the target antigen.

DR. DILIBERTI: Charlie Diliberti, Barr

Labs.

When a brand manufacturer makes a process change, and that change is deemed significant enough to warrant follow-up immunogenicity studies, what is the typical trial design? Is it a head-to-head, pre-change versus post-change? Is it a historical control? And if it is historical control, how valid is that, even though the same assay may have been used? Maybe the assay has some drift over time.

And finally, what are the typical acceptance criteria that are used? Are they equivalence criteria, are they non-inferiority? Particularly in the case of rare immunogenic events, low-frequency events.

DR. ROSENBERG: Most of the studies that we've asked for have been head-to-head comparison.

DR. GERRARD: But in my experience, most are not really powered to pick up subtle differences. You know, I mean, let's be honest here. You know, if you test 50 to 100 patients, that's not going to pick up a delta of a very small

change.

DR. ROSENBERG: Of course it's not.

DR. GERRARD: No.

DR. ROSENBERG: And that's why we ask for post-marketing studies, as well. And I think you have to have a reasonable assurance. And where your comfort level lies is in some ways arbitrary unless--For instance, if you have a one-in-10,000 incidence of PRCA, and you do a 1,000-patient immunogenicity study, you're not likely to see an event, if the products are comparable. But in that case, you can ask for post-marketing studies that would cover that number of patients.

So I think it's a question of where your comfort level lies, given what the incidence of the adverse event is pertaining to immunogenicity, of an innovator or of another similar product.

DR. DILIBERTI: Are there any particular statistical acceptance criteria that are typically applied? Or are no criteria applied, and the data are just evaluated for a comfort level once they are obtained?

DR. ROSENBERG: No, I mean, we certainly try and apply statistical principles where they're appropriate to do so.

DR. DILIBERTI: So what sorts of acceptance criteria are typically applied?

DR. ROSENBERG: I think I would have to go back and get that information for you. I'm not a statistician.

DR. DILIBERTI: Would you be able to post that onto the docket, please?

DR. ROSENBERG: I think we can do that.

DR. DILIBERTI: Great. Thank you.

DR. STEIN: I would just add that I don't think immunogenicity studies have been requested in isolation just to get better immunogenicity data; but additional safety data and PK data have often been requested along with that. And that's the bottom line.

DR. VELAGAPUDI: Hi. This is Raja Velagapudi, from Barr Laboratories.

I've been looking at the various cases and arguments. It occurs to me, and I'm, you know,

like a pharmaco-clinicist [ph] always--My theory is to the numbers. You have cases of low incidence of immunogenicity for some products. And you have cases of low incidence and low grade immunity, immunogenicity. And you have high incidence and high immunogenicity; means like it's locking out the molecule type of thing. So I see it as three distinct groups of immunogenic reactions here.

And to me, it's unfair to try to force the doors open and then lock safe drugs out with this unnecessary burden for the cases of low-grade immunity and--you know, like not affecting the clinical efficacy type of molecules.

You have low-end molecules where really immunogenicity is not a significant clinical relevance. They are due to the nature of the protein that occurs, but really not significantly affecting. And those should be treated differently from highly immunogenic, high incidence, and effective things. And the testing should be different; not putting everything in one basket and making everybody follow the same thing.

DR. ROSENBERG: I think that our approach is a risk-based approach. And that only in part is based on the history of the innovator's product.

So for a product such as GCSF, which was used as the example of one where you rarely to never see an immune response, that is the factor that is solely involved in generation of white blood cells. And when you knock it out from the mouse, they are profoundly neutropenic.

And we certainly haven't seen immunogenicity neutralizing antibodies in humans; although it's seen in dogs. But in general, that product is used in very neutropenic patients, patients whose immune systems are compromised.

And the fact that it is such a safe drug is wonderful. And it would be, I think, unconscionable not to test a follow-on for the potential to generate immune responses that would cause neutralization of a factor that is absolutely essential for biological functioning. Products have to be safe. And with their inherent biological activity, their biological function is a

key factor in determining what the risk is from immune responses.

DR. VELAGAPUDI: Yes.

DR. GERRARD: But he raises an interesting question, as far as, should the focus be not on just comparisons of immunogenicity, but the way I interpreted it was immunogenicity with clinical consequences.

So let's say you had two products and they had different immunogenicity, but neither one had clinical consequences. So that doesn't matter? What would be the approach?

DR. VELAGAPUDI: That's my point, you know. Like on the low end molecules, like which are on the less immunogenicity scale.

DR. GERRARD: And I think this is a concern as assays improve, because are we always going to be able to perhaps detect the lower affinity, the transient--You know, you're always going to see something.

DR. STEIN: I think, in reality, we don't know the answer to the question, because there

haven't been good studies. If antibody formation causes a safety problem, you hear about it; you study it; you know what the correlation is. But not all patients respond to all products.

And nobody, at least that I am aware of, has actually done an adequate study to compare patients who respond and the patients who don't respond with antibodies and look for a correlation on a meaningfully powered study. So I don't think we know the answer to the question about whether there's loss of efficacy because of antibody formation.

DR. ROSENBERG: Right. But I think also some data that even Robin showed this morning would indicate that when you look at patients who are, for instance, non-responders to an Interferon drug, that a very high percentage of those patients are antibody responders. I mean, there are data that certainly have spoken to the issue.

DR. GERRARD: But I'm saying what if there is no [inaudible].

DR. ROSENBERG: Right, okay, but then the

burden is that you've done a big enough study that you've seen enough patients, and that you have observed that there is no clinical effect. And that requires a substantial experience. And that's not something that I think you can get away with in a very limited trial.

I agree, it's important to know. It's also important to look for it. And I think we haven't looked for it in the right way. I mean, I think we have to really do better studies than we've done. We have to look at the duration of response. We have to look at whether the response tolerizes over time.

As was mentioned with the Beta Interferon, it's a single gene encoding for that. Is there a long-term consequence to neutralizing that? I don't think anybody has looked for that. So I think you're right, but I think you have to do a big enough study to have confidence that in fact you can say there is no clinical effect.

DR. VELAGAPUDI: My intuition is that it's like not all products will have same kind of

clinical impact. There are products that you know from the labeling that will have significant clinical impact. And from the experience and the literature and the labeling and everything, you know certain products have least clinical relevance. Not that they're non-existent; they're the least clinical relevance. There are products that have high significance.

So the degree of testing you do, in my view, will be different. One is like a product characterization type of thing, to see if things exist with this product; versus how much is actually clinically relevant, is another one that you are looking at. So I want you to consider that.

DR. ROSENBERG: Okay. Last two comments.

DR. DILIBERTI: Charlie Diliberti, Barr Labs.

We've heard a lot about FDA's risk-based approach. And it's, I think, a very sensible approach, that I fully support. One of the things that we heard about yesterday was to determine what

is the denominator? We've heard a lot about the numerator, about all of the anecdotal accounts of immunogenic reactions that have clinical consequences. The question is, what's the denominator?

And in relation to that, and sort of as a follow-up to Raja's question, has FDA looked across the board? Because FDA is the holder of all of the data on all of the products. Has FDA looked across the board to try to, in a sense, classify groups of products or individual products as to high risk, medium risk, intermediate risk, low risk? Because I think that may help us to design the trials appropriately to address those risks and minimize them.

DR. ROSENBERG: I think that's a good point. And we certainly have done that and--I mean, I don't know if we published the totality of it, but we've certainly published some papers that have contained examples of that. And I think that we certainly, within our division, do that kind of an analysis. But I should say we are working on an

immunogenicity guidance document that will be containing that kind of information.

DR. DILIBERTI: Thank you.

DR. GERRARD: Yes, I think that's important. Because I think too often companies working with just a few products see things in isolation; and not look at similar issues that have occurred with other products. So you get half the world believes that pegylation [ph] causes immunogenicity, and the other half believe pegylation reduces immunogenicity. Neither may be true; but unless you actually look in a systematic way at all proteins and look at a number of other factors that may be contributing, you never come up with the right answer.

DR. ROSENBERG: Inger, would you like to bring us home?

DR. MOLLERUP: I can try. Inger Mollerup, Novo Nordisk.

I'd like to go back to Dr. Gerrard's comment about the product today not being equal to the process. And I was somewhat surprised at the

confidence with which you stated that.

I'd like to go back to the slide Steve Kozlowski put up yesterday on the iceberg; that there is this chunk of the iceberg we can account for with the analytics; there's this part of the iceberg we can account for with characterization and everything else we know; but there's still a part of the iceberg that's related to the process. And I think that's still why, looking at comparability exercises within innovator processes when we do manufacturing changes, they are actually huge tasks. They are cumbersome. And that comes for a good reason.

And as Amy said, sometimes that does imply doing an immunogenicity study. And I think at the end of the day, the jump to go from all that platform of data and to a follow-on biologic--I guess my conclusion is that, yes, I would certainly support that these trials, immunogenicity trials, be done head-to-head, and prior approval. Because there is a risk that needs to be addressed.characterization

DR. ROSENBERG: I think that we will bring this session to a close. We'll start up again at 3:30. So thank you very much, all. It was an

excellent session.

[Whereupon, at 2:59 p.m., the session was concluded.]

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